

REMARKS**Amendments to the Claims**

Claims 1-22 are pending. The Applicant respectfully asks the Examiner to replace all prior versions and listings of claims in the present application with the listing of claims currently provided. Claims 1-5, 7-11, 18-20 and 22 were amended; Claims 6, 15-17 and 21 were canceled; Claims 23-37 are new. The Applicant hereby states that all amendments do not add new subject matter to the specification.

Support for Claims directed, in part, toward non-cancerous melanin related afflictions, non-cancerous skin pigmentation disorders and melanin related disorders which is not a melanoma can be found, *e.g.*, on pg. 2, lines 14-22; pg. 21, lines 11-24, and Example 1.

Support for Claims directed, in part, toward a patient in need thereof can be found, *e.g.*, on pg. 23, lines 8-14; pg. 37, lines 28-31; pg. 38, lines 17-30; and Example 1, 3-7.

Support for Claims directed, in part, toward administering a botulinum toxin in the vicinity of a skin region exhibiting a symptom of the melanin related affliction can be found, *e.g.*, on pg. 19, lines 12-24; pg. 38, lines 1-15; and Examples 1-7.

Support for Claims directed, in part, toward alleviating a symptom of a skin pigmentation disorder symptom can be found, *e.g.*, on pg. 21, lines 26-31; pg. 22, lines 14-19; pg 45, lines 8-14; and Examples 1-7.

Support for Claims directed, in part, toward increasing pigmentation in a melanin related affliction associated with decreased pigmentation, or decreasing pigmentation in a melanin related affliction associated with increased pigmentation can be found, *e.g.*, on pg. 21, lines 26-31; pg. 22, lines 14-19; and pg 45, lines 8-14; and Examples 1-7.

Support for Claims directed, in part, toward administering about 0.001 units/kg to about 35 units/kg of patient body weight can be found, *e.g.*, on pg. 19, lines 23-32.

Claim Objections

The Examiner has objected to Claim 1 pursuant to 37 C.F.R. § 1.175 as being a substantially duplicate of Claim 22 because while Claim 22 recites the term "native," and Claim 1 does not, the administered botulinum toxins cover the same thing. The Applicant respectfully submits that amended Claim 1 is definite and respectfully requests withdrawal of the objection.

The Examiner has objected to Claim 7 because Claim 7 depends on Claim 16 and a dependant claim should depend from a prior claim and not from a later presented claim. The Applicant respectfully submits that amended Claim 7 is definite and respectfully requests withdrawal of the objection.

Rejection Pursuant to 35 U.S.C. § 112, ¶ 2 Definiteness***Claims 2-4 and 18-21***

The Examiner has rejected Claims 2-4 and 18-21 as allegedly being indefinite pursuant to 35 U.S.C. § 112, ¶ 2 arguing that the claim limitations are contradictory. Specifically, the Examiner contends that the claimed method is not clearly or distinctly claimed because the administration of the same composition to the same location in the same dose can not result in two divergent effects when administered to the same patient with the same melanin related affliction. The Applicant respectfully asks for reconsideration pursuant to 37 C.F.R. § 1.111.

The Applicant respectfully submits that amended Claims 2-4 and 18-21 are definite and respectfully request withdrawal of the 35 U.S.C. § 112, ¶ 2 indefinite rejection.

Claims 8-10

The Examiner has rejected Claims 8-10 as allegedly being indefinite pursuant to 35 U.S.C. § 112, ¶ 2 arguing that the claim limitations are contradictory. Specifically, the Examiner contends that the claimed method is not clearly or distinctly claimed because the administration of the same composition to the same location in the same dose can not result in two divergent effects when administered to the same patient with the same melanin related affliction. The Applicant respectfully asks for reconsideration pursuant to 37 C.F.R. § 1.111.

The Applicant respectfully submits that amended Claims 8-10 are definite and respectfully request withdrawal of the 35 U.S.C. § 112, ¶ 2 indefinite rejection.

Claim 15

The Examiner has rejected Claim 15 as allegedly being indefinite pursuant to 35 U.S.C. § 112, ¶ 2 arguing that the claimed method is not distinctly claimed in light of the fact that the prior art teaches botulinum toxin to prevent hair loss and not enhance hair removal. The Applicant respectfully asks for reconsideration pursuant to 37 C.F.R. § 1.111.

Claim 15 was canceled. The Applicant submits that the cancellation of Claim 15 was for reasons other than patentability in general or with regards to the current indefiniteness rejection. However, cancellation of Claim 15 has rendered the indefiniteness rejection moot. Thus, the Applicant respectfully requests withdrawal of the 35 U.S.C. § 112, ¶ 2 indefinite rejection against Claim 15.

Claim 16

The Examiner has rejected Claim 16 as allegedly being indefinite pursuant to 35 U.S.C. § 112, ¶ 2 arguing that the phrase "present as a skin area having a distinct color and size" modifies the preamble and not the administering step. The Applicant respectfully asks for reconsideration pursuant to 37 C.F.R. § 1.111.

Claim 16 was canceled. The Applicant submits that the cancellation of Claim 16 was for reasons other than patentability in general or with regards to the current indefiniteness rejection. However, cancellation of Claim 16 has rendered the indefiniteness rejection moot. Thus, the Applicant respectfully requests withdrawal of the 35 U.S.C. § 112, ¶ 2 indefinite rejection against Claim 16.

Rejection Pursuant to 35 U.S.C. § 101 Obviousness-type Double Patenting

The Examiner has provisionally rejected Claim 1 and 22 as allegedly being unpatentable over Claims 40 and 45 of Stephan Donovan, *Method for Treating Cancer with a Neurotoxin*, U.S. Patent Application Serial No. 10/929,040, hereafter "the Donovan application," under the judicially created doctrine of obviousness-type double patenting pursuant to 35 U.S.C. § 101. Specifically, the Examiner contends that the conflicting claims are not patentably distinct from each other because they are all directed toward treating a melanoma. The Applicant respectfully asks for reconsideration pursuant to 37 C.F.R. § 1.111.

The Applicant respectfully submits that amended Claims 1 and 22 are directed, in part, towards treating a non-cancerous melanin related affliction in a patient in need thereof. As such, the presently claimed methods are patentably distinct from the Donovan application because a melanoma is a cancer. Thus, the Applicants respectfully request withdrawal of the 35 U.S.C. § 101 obviousness-type double patenting rejection for Claims 1 and 22.

Rejection Pursuant to 35 U.S.C. § 102(b) Anticipation

The Examiner has rejected Claims 1-6, 11-14, 16-22 as allegedly being anticipated pursuant to 35 U.S.C. § 102(b) by Maria Rodriguez Vazquez et al., *Eccrine Naevus: Case Report and Literature Review*, 82(2) Acta Derm. Venereol. 154-156 (2002), hereafter "the Vazquez reference." The Applicant respectfully asks for reconsideration pursuant to 37 C.F.R. § 1.111.

The presently claimed methods are directed toward treating 1) a non-cancerous melanin related affliction in a patient in need thereof (Claim 1); 2) a non-cancerous skin pigmentation disorder in a patient in need thereof (Claim 5); and 3) a melanin related affliction, which is not a melanoma, in a patient in need thereof (Claim 18) by administering a botulinum toxin. A melanin related affliction is defined as a disease, disorder, problem and/or a cosmetically undesirable state or condition in an individual which is controlled or influenced by the present or absence of melanin, see, pg. 21, lines 11-14. The Vazquez reference does not anticipate the presently claimed methods because this reference does not teach a method for treated a non-cancerous melanin related affliction, a non-melanoma melanin related affliction or a skin pigmentation disorder in a patient in need thereof.

First, the Applicant respectfully submits that the Vazquez reference does not disclose a method of treating a melanin related affliction as presently claimed, but instead discloses a method of treating the excessive sweating associated with eccrine nevus. Eccrine nevus is an eccrine sweat gland disorder characterized by rare benign lesions resulting from an increased number and enlarged size of normal appearing eccrine sweat glands, see, e.g., John C. Kawaoka et al., *Eccrine nevus*, J. Am. Acad. Dermatol. 51(2) 301-304 (2004) at pg. 310, col. 2, ¶ 3. This abnormal sweat gland growth is the underlying secondary cause of hyperhidrosis (i.e., abnormal excessive sweating), *Id.* at pg. 310, col. 1, ¶ 4. The Vazquez reference discloses a use of a botulinum toxin to treat a patient with eccrine nevus, see, pg.154, col. 1, ¶ 2, lines 1-5. This reference discloses that the use of botulinum toxin to treat the excessive sweating "resulted in a reduction of more than 50% of sweat by 6 months," see, pg. 155, col. 1, ¶ 1, lines 3-5. Thus, the Vazquez reference discloses a method of treating excessive sweating in a patient diagnosed with eccrine nevus by administering a botulinum toxin. As such, the Vazquez reference does not anticipate a method for treating a melanin related affliction by administering a botulinum toxin as presently claimed.

Second, the Applicant respectfully submits that the Vazquez reference does not discloses a melanin related affliction. The Vazquez reference discloses that a patient suffering from excessive sweating due to eccrine nevus "had slight hyperpigmentation without epidermal alterations" in the affected region, see, pg. 154, col. 1, ¶ 4, lines 1-3. At best, the term "hyperpigmentation" means an increased pigmentation of the skin. However, the underlying

cause for this hyperpigmentation was never disclosed by the Vazquez reference. Although the Examiner's assumption is that hyperpigmentation reported in this reference was due to the production on melanin, it is equally as plausible, if not more so, that this hyperpigmentation was due to a non-melanin process such as, e.g., 1) skin discoloration due to staining from excessive sweat; 2) skin discoloration due to increased vascularization known to occur in eccrine nevus; or 3) skin discoloration due to overgrowth of the underlying eccrine sweat glands in the dermis that push through the skin forming papulae. In fact, a non-melanin process is supported by the Vazquez reference itself, which reported that histological examination of a tissue biopsy revealed no epidermal changes, see, pg. 154, col. 1, ¶ 6, lines 1-3. Hyperpigmentation due to melanin would reveal increase melanin deposits in the epidermis, and thus, an epidermal change. Thus, although disclosing the term "hyperpigmentation," the Vazquez reference did not disclose that the hyperpigmentation was an undesirable state or condition in an individual which is controlled or influenced by the present or absence of melanin. As such, the Vazquez reference does not anticipate a method for treating a melanin related affliction by administering a botulinum toxin as presently claimed.

Lastly, even if the term "hyperpigmentation" as disclosed in the Vazquez reference was due to an increase deposit of melanin, this reference still does not inherently anticipate a method of treating a melanin related affliction as presently claimed.

According to *MPEP* 2112.IV,

[T]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. . . . To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.'

The presently claimed methods are directed, in part, toward treating melanin related afflictions in a patient in need thereof. The recite phrase "in a patient in need thereof" is an expressed limitation. Thus, in order for the Vazquez reference to anticipate, it must teach

that a botulinum toxin treatment was administered to a patient for the reason of treating a melanin related affliction as presently claimed. It does not. The Vazquez reference only discloses the use of a botulinum toxin for the treatment of excessive sweating, see, pg. 155, col. 1, ¶ 1, lines 3-5. In support of this reference's explicit statement, the Vazquez reference also indicates that a treatment "with 20% aluminum chloride hexahydrate in absolute alcohol was not effective," see, pg. 154, col. 1, ¶ 6, line 1 through pg. 154, col. 2, ¶ 1, line 1. ACH treatment is a standard treatment for the excessive sweating caused by hyperhidrosis. Although the Vazquez reference mentions that the region affected with eccrine nevus was slightly hyperpigmented, this reference is absolutely silent with respect to whether the botulinum toxin treatment was also performed in this patient to reduce the hyperpigmented area, and whether such a treatment was effective in treating hyperpigmentation. Furthermore, in the fewer than 20 eccrine nevi cases reported in the literature, most present with no hyperpigmentation at all, see, e.g., John C. Kawaoka et al., *Eccrine nevus*, J. Am. Acad. Dermatol. 51(2) 301-304 (2004) at pg. 310, col. 2, ¶ 3. Thus, a person of ordinary skill in the art would not even recognize that the botulinum toxin treatment for eccrine nevus as disclosed in the Vasquez reference would be a treatment directed toward hyperpigmentation because hyperpigmentation is not normally found associated with eccrine nevus.

The May 5, 2006 Office Action states on pg. 5, ¶ No. 12 that "while the Vasquez reference is silent with respect to color changes in the skin or hair, the Applicants disclosure provides definitions and evidence that botulinum toxin when administered to hyperpigmented skin and hair produces pigmentation effects." The Applicant respectfully submits that the use of the Applicants disclosure to support an inherency claim is inappropriate. According to *MPEP* 2112.IV, "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic **necessarily flows from the teachings of the applied prior art.**" Thus, the use of the present specification as a basis of fact or technical reasoning is prohibited.

Thus the extrinsic evidence from the Vazquez reference and the knowledge of a person of ordinary skill in the art does not make it clear that an administration of a botulinum toxin

would be useful for treating hyperpigmentation, let alone a melanin related affliction. Furthermore, a person of ordinary skill in the art would not recognize that administration of a botulinum toxin would be useful in treating a melanin related affliction as presently claimed because 1) hyperpigmentation is not normally associated with eccrine nevus cases, 2) the Vazquez reference only treated the hyperhidrosis associated with eccrine nevus, and 3) the Vazquez reference did not even report whether the botulinum treatment affected the hyperpigmentation of the skin. As such, the Vazquez reference does not anticipate a method for treating a melanin related affliction by administering a botulinum toxin as presently claimed.

Claims 2-4, 11-14, 16, 17, 19, 20 and 22 are all dependent on one of Claims 1, 5 and 18 and as such, are also directed toward a method for treating a melanin related affliction, a skin pigmentation disorder or hair color pigmentation in a patient in need thereof. Additionally, Claims 6, 16 and 21 were canceled. Thus, the Vazquez reference does not read on these claims for the reasons given above.

Therefore, the Applicant respectfully submits that the pending claims are not anticipated by the Vazquez reference and respectfully request withdrawal of the 35 U.S.C. §102(b) anticipation rejection for Claims 1-6, 11-14, 16-22.

Rejection Pursuant to 35 U.S.C. § 102(e) Anticipation

The Waugh Publication

The Examiner has rejected Claims 1-14 and 16-22 as allegedly being anticipated pursuant to 35 U.S.C. § 102(e) by Jacob Waugh and Michael Drake, *Multi-Component Biological Transport Systems*, U.S. Patent Publication 2004/0220100 (filed Mar. 3, 2004), hereafter "the Waugh publication." The Applicant respectfully asks for reconsideration pursuant to 37 C.F.R. § 1.111.

According to MPEP § 2131, for a reference to anticipate a pending claim, that reference must teach each and every element of the pending claim.

The presently claimed methods are directed toward treating 1) a non-cancerous melanin related affliction in a patient in need thereof (Claim 1); 2) a non-cancerous skin pigmentation disorder in a patient in need thereof (Claim 5); 3) hair color pigmentation in a patient in need thereof (Claim 8); and 4) a melanin related affliction, which is not a melanoma, in a patient in need thereof (Claim 18) by administering a botulinum toxin. The present specification defines a melanin related affliction as a disease, disorder, problem and/or a cosmetically undesirable state or condition in an individual which is controlled or influenced by the present or absence of melanin, see, pg. 21, lines 11-14. The Waugh publication does not anticipate the presently claimed methods because this publication does not teach a method for treated a non-cancerous melanin related affliction, a non-melanoma melanin related affliction, a skin pigmentation disorder or hair color pigmentation in a patient in need thereof.

First, the Applicant respectfully submits that, contrary to the Examiners contention, ¶ 18 of the Waugh publication does not disclose a melanin related affliction, instead this paragraph discloses wrinkles. For example, ¶ 18 indicates that the appearance of wrinkles can be "caused by biochemical, histological, and physiologic changes that accumulate from environmental damage[,] . . . the constant pull of gravity, frequent and constant positional pressure on the skin (i.e., during sleep), and repeated facial movements caused by the contraction of facial muscles." Wrinkles result from the thinning of the dermis with age due to the diminishment of collagen and hyaluronic acid in the skin, see, e.g., Jennifer Clay Cather et al., *Update of Botulinum Toxin for Facial Aesthetics*, 20 Dermatol. Clin. 749-761 (2002) at pg. 751, col 2, ¶ 2, lines 12; and Arnold W. Klein, *Treatment of Wrinkles with BOTOX*, 30 Curr. Problems Dermatol. 188-217 (2002) at pg. 191, ¶ 3, lines 1-4. Thus, wrinkles are not a disease, disorder, problem and/or a cosmetically undesirable state or condition in an individual which is controlled or influenced by the present or absence of melanin. As such, ¶ 18 of the Waugh publication does not disclose either a melanin related affliction or a method for treating such an affliction as presently claimed.

Likewise, the alleged disclosure in the Waugh publication of a method for treating acne found at ¶ 9, ¶ 43 ¶ 135 and ¶ 136 does not anticipate the presently claimed methods because, although a skin disorder, acne is not a melanin related affliction. Acne is an

inflammatory disease of the sebaceous glands and hair follicles of the skin that occurs when the pores of the skin become clogged with oil, dead skin cells, and bacteria. Acne is thought to be caused by the interplay of four factors 1) excessive sebum production secondary to sebaceous gland hyperplasia; 2) obstruction of the hair follicle due to abnormal keratinization of the follicular keratinocytes that prevents normal shedding; 3) accumulation of lipids and cellular debris within the blocked follicle; and colonization of *Propionibacterium acnes*, which provokes an immune response resulting in inflammation. Inflammation is further enhanced by follicular rupture and subsequent leakage of lipids, bacteria, and fatty acids into the dermis, see, e.g., Aamir Haider and James C. Shaw, Treatment of Acne Vulgaris, 292(6) JAMA 726-735 (2004) at pg. 727, col. 1, ¶ 3; Dana L. Suskind et al., *Botulinum Toxin in the Treatment or Prevention of Acne*, U.S. Patent Publication 2005/0074466 (Apr. 7, 2005) at ¶ 5. In fact, the Waugh publication expressly states this pathogenesis in ¶ 9 when it discloses that paralysis due to botulinum toxin "blocks [synoptic transmission] signals that normally would cause . . . overexcretion such as hyperhidrosis or acne." Thus, acne is not a disease, disorder, problem and/or a cosmetically undesirable state or condition in an individual which is controlled or influenced by the present or absence of melanin. As such, ¶ 9, ¶ 43 ¶ 135 and ¶ 136 of the Waugh publication does not disclose either a melanin related affliction or a method for treating such an affliction as presently claimed.

The Waugh publication disclosure at ¶ 16, cited by the Examiner, refers to a general description of the composition of the dermis layer of the skin. This disclosure is silent with respect to either a melanin related affliction or a method for treating such an affliction. Likewise, Waugh publication disclosure at ¶ 21, ¶ 144 and ¶ 146, although related to the multi-component biological transport system taught by this publication, offer no teaching regarding either a melanin related affliction or a method for treating such an affliction. For example, both the Waugh publication and the present application teach the use of a topical administration of a pharmaceutical composition. However, the Waugh publication does not teach the use of such pharmaceutical composition in treating a melanin related affliction, a skin pigmentation disorder or hair color pigmentation in a patient in need thereof. In addition, the disclosure relating to "antioxidants," "coloring agents," "conditioning agents," "darkening or lighting agents" and "sunblocks," are secondary additives "in addition to

botulinum toxin, insulin or other biologically active agent and carrier.” See ¶ 144. Thus, this disclosure does not teach the use of a botulinum toxin (the biologically active agent) in modulating melanin production.

Claims 2-4, 7, 9-11, 17, 19, 20 and 22 are all dependent on one of Claims 1, 5, 8 and 18 and as such, are also directed toward a method for treated a melanin related affliction, a skin pigmentation disorder or hair color pigmentation in a patient in need thereof. Additionally, Claims 6, 15, 16 and 21 were canceled. Thus, the Waugh publication does not read on these claims for the reasons given above.

Therefore, the Applicant respectfully submits that the pending claims are not anticipated by the Waugh publication and respectfully requests withdrawal of the 35 U.S.C. §102(e) anticipation rejection for Claims 1-14 and 16-22.

The Pastan Publication

The Examiner has rejected Claims 1, 2, 4-7, 11, 12, 14 and 16 as allegedly being anticipated pursuant to 35 U.S.C. § 102(e) by Ira Pastan et al., *XAGE-1, A Gene Expressed in Multiple Cancers, and Uses Thereof*, U.S. Patent Publication 2004/0087772 (filed Aug. 31, 2001), hereafter “the Pastan publication.” The Applicant respectfully asks for reconsideration pursuant to 37 C.F.R. § 1.111.

According to *MPEP* § 2131, for a reference to anticipated a pending claim, that reference must teach each and every element of the pending claim.

As discussed above, the presently claimed methods are directed, in part, toward treating a non-cancerous melanin related affliction, a non-cancerous skin pigmentation disorder or hair color pigmentation, in a patient in need thereof by administering a botulinum toxin.

The Pastan publication discloses a method of inhibiting growth of a cancer cell expressing XAGE-1 p9 or XAGE-1 p16 proteins by contacting the cells with immunoconjugates comprising an anti-p9 or anti-p16 antibody and a toxin moiety, see, e.g., abstract; ¶ 23; and

Claims 85-90. The Pastan publication identifies certain types of cancers useful for the disclosed method, including melanoma, but no other skin cancers, see Table 1. Thus, the Pastan publication does not anticipate the presently claimed methods because this publication does not teach a method for treated a non-cancerous melanin related affliction, a non-cancerous skin pigmentation disorder or hair color pigmentation, in a patient in need thereof.

Claims 2, 4, 7, 11, 12 and 14 are all dependent on one of Claims 1, 5 and 8 and as such, are also directed toward a method for treated a melanin related affliction, a skin pigmentation disorder or hair color pigmentation in a patient in need thereof. Thus, the Pastan publication does not read on these claims for the reasons given above. Additionally, Claims 6 and 16 were canceled.

Therefore, the Applicant respectfully submits that the pending claims are not anticipated by the Pastan publication and respectfully requests withdrawal of the 35 U.S.C. §102(e) anticipation rejection for Claims 1, 2, 4-7, 11, 12, 14 and 16.

CONCLUSION

For the above reasons the Applicants respectfully submit that the claims are in condition for allowance, and the Applicants respectfully urge the Examiner to issue a Notice to that effect. Should there be any questions, the Examiner is invited to call the undersigned agent.

Please use Deposit Account 01-0885 for the payment of any extension of time fees pursuant to 37 C.F.R. § 1.136 or any other fees due in connection with the current response.

Respectfully submitted,

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